REMARKS

STATUS OF CLAIMS

Claims 1, 3-15, and 69-95 were pending in the application, and all claims are rejected by the Examiner under 35 U.S.C. § 112, first paragraph, as allegedly non-compliant with the written description requirement and under 35 U.S.C. § 112, second paragraph, as allegedly failing to set forth the subject matter which applicants regard as their invention. Claims 1, 3-4, 6, 8-15, 69-71, and 92 are rejected under 35 U.S.C. § 102(b) as being anticipated by both Khosla et al. (US Patent No. 6,066,721)("Khosla et al.") and Katz et al. (US Patent No. 6,004,787)("Katz et al."). Claims 1, 3-15, 69-71, 74-75, 77-82, and 85-95 are rejected as being unpatentable under 35 U.S.C. § 103(a) over Katz et al. in view of Kim et al. (Gene, 199:293-301 (1997))("Kim et al.").

While Applicants respectfully submit that all of above rejections are entirely without merits, claims 1, 76, 85, 86, 88, 91, and 93-95 have been amended to expedite the prosecution without prejudice to possible future prosecution of these claims in their current state. In particular, claim 1 is amended by adding a definition of the term "reference polypeptide segment" and the term "naturally occurring polyketide synthase (PKS)," for which the support is found in the specification, at least in Table 12 and related text, as has also been impliedly acknowledged in the Examiner's Interview Summary dated October 17, 2007 (*Cf.* claim 92 presented previously). Claim 1 is also amended by changing the relationship between the conditions e) and f) from "or" to "and"; so are claims 86, 88, 91, and 93-95 amended similarly. The support for these amendments is found at least in the originally filed claims 6 and 7, as well as in paragraph [0335] of the instant application. Claim 76 is amended to correct the language informalities. Claim 85 is changed from independent to dependent from claim 1 while deleting various common limitations between the two claims. Therefore, the amendments do not introduce any new matter.

In addition to claims 2 and 16-68, which were cancelled previously, claims 6-7, 75, 77-78, and 90 are now cancelled. Therefore, upon entry of this paper, claims 1, 3-5, 8-15, 69-74, 76, 79-89, and 91-95 are pending for examination.

Entry of this paper and reconsideration of the rejections are respectfully requested in view of the claim amendments above and the following remarks.

THE INVENTION

The instant invention is drawn in general to synthetic polyketide synthase ("PKS") genes or segments thereof, which differ from the naturally occurring PKS genes or segments significantly in the nucleotide sequence while retaining comparable activity to that of the naturally occurring PKS genes or segments, respectively.

More specifically, the instant invention is drawn, in one aspect, to a synthetic gene encoding a polypeptide segment, wherein said polypeptide segment corresponds to a reference polypeptide segment encoded by a naturally occurring polyketide synthase (PKS) gene, wherein said reference polypeptide segment is selected from any polypeptide segments of said naturally occurring PKS and said naturally occurring PKS is selected from the group consisting of erythromycin PKS, megalomicin PKS, oleandomycin PKS, pikromycin PKS, niddamycin PKS, tylosin PKS, pimaricin PKS, pte PKS, avermectin PKS, oligomycin PKS, nystatin PKS, and amphotericin PKS, and

a) the polypeptide segment encoded by the synthetic gene and the polypeptide segment encoded by the naturally occurring gene are the same length and comprise at least 50 amino acids;

b) the polypeptide segment encoded by the synthetic gene and the polypeptide segment encoded by the naturally occurring gene are at least 95% identical in amino acid sequence;

c) the polypeptide segment-encoding sequence of the synthetic gene and the polypeptide segment-encoding sequence of the naturally occurring gene are less than 90% identical in nucleotide sequence;

d) the polypeptide segment encoded by the synthetic gene retains the activity of the polypeptide segment encoded by the naturally occurring gene;

e) the polypeptide segment-encoding sequence of the synthetic gene is free from at least one Type IIS enzyme restriction site present in the polypeptide segment-encoding sequence of said naturally occurring gene; and

f) the polypeptide segment-encoding sequence of the synthetic gene is different from the polypeptide segment-encoding sequence of said naturally occurring PKS gene and comprises at least two of:

i) a Spe I site near the sequence encoding the amino-terminus of the module;

ii) a Mfe I site near the sequence encoding the amino-terminus of a KS domain;

iii) a Kpn I site near the sequence encoding the carboxy-terminus of a KS domain;

iv) a Msc I site near the sequence encoding the amino-terminus of an AT domain;

v) a Pst I site near the sequence encoding the carboxy-terminus of an AT domain;

vi) a BsrB I site near the sequence encoding the amino-terminus of an ER domain;

vii) an Age I site near the sequence encoding the amino-terminus of a KR domain;

viii) an Xba I site near the sequence encoding the amino-terminus of an ACP domain.

ARGUMENTS

I. Rejection Under 35 U.S.C. § 112, First Paragraph (Written Description) Should Be Withdrawn.

The Examiner rejected claims 1, 3-15 and 69-95 under 35 U.S.C. § 112, first paragraph, as allegedly "containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention."

The Examiner made the sweeping rejections based on a number of disjointed assertions, which Applicants endeavor to summarize as follows: (1) "the claims do not set forth said 'reference polypeptide' and are devoid of a structure"; (2) "no functional limitation is recited in the claims for the recited 'polypeptide segment' described as being 90% or less or at least 95%, thus no correlation is made between function and structure"; (3) "there is no indicia as to what said segment looks like or the reference structure"; (4) "the claims encompass a large variable genus, not adequately described"; (5) "[t]he specification fails to provide any additional representative species of the claimed genus to show that application was in possession of the claimed genus"; (6) as for claim 92, "the disclosure does not provide a description of said structure, just the accession numbers"; (7) "[t]he claimed genus could include non-functional proteins or proteins with a different function than the one contemplated"; and (8) "[t]he skilled artisan cannot envision the detailed chemical structure of the encompassed genus of genes and the encoded polypeptide." (Final Office Action, pages 3-5).

The Examiner's assertions (1), (3), (6), and (8) are essentially the same, or closely related, and seemingly form the Examiner's first argument: (A) the term "reference polypeptide

segment" in claim 1 is not clearly defined because the structure of the reference polypeptide or the synthetic gene is not specifically disclosed. Assertion (2) seems to be the Examiner's second argument: (B) the claims do not satisfy the written description requirement under 35 U.S.C. § 112, first paragraph, due to Applicants' failure to include a functional limitation for the recited "polypeptide segment" in the claims and failure to disclose the correlation between the function and structure of the "polypeptide segment." Assertions (4) and (7) seem to form the Examiner's third argument: (C) the claims do not satisfy the written description requirement because they have such a broad scope as to include non-functional species or species with different functions. Assertion (5) seems to be the Examiner's fourth argument: (D) the claims do not satisfy the written description requirement for Applicants' failure to disclose certain "additional representative species." Applicants will address each of the Examiner's arguments in turn.

(A) The Examiner's first argument is that claim 1 contains a phrase "reference polypeptide" not specifically defined in the claim, which, as Applicants understand it, is the core of the concerns articulated by the Examiner. Essentially, the Examiner interprets 35 U.S.C. § 112, first paragraph, as requiring Applicants to specifically describe the structure of the "reference polypeptide segment." However, this interpretation is neither accurate nor realistic in the context of the instant application. Applicants have submitted previously that a person of ordinary skill in the art would be able to understand that the "reference polypeptide segment" in claim 1 refers to any polypeptide segment of a naturally occurring polyketide synthase (PKS), which in turn is encoded by a naturally occurring PKS gene. The specification teaches that the amino acid sequences of naturally occurring PKSs and the corresponding genes encoding these PKS sequences are known, for example, from various databases such as Swissprot, Genbank, and BLAST (*see* paragraphs [0178] and [0352]), because these sequence structures are readily retrievable through the accession numbers provided. In the specification, Applicants have also provided examples of various naturally occurring PKSs and the genes encoding these naturally occurring PKSs. Because a claim cannot be read in vacuum but must be read in light of specification, it should be clear to a person of ordinary skill in the art from the language of claim 1 and the specification of this application what the "reference polypeptide segment" refers to.

"The specification need not disclose what is well-known to those skilled in the art and preferably omits that which is well-known to those skilled and already available to the public." MPEP § 2164.05. The specification of this application has provided adequate information for a

person of ordinary skill in the art to access the amino acid and nucleotide sequences of naturally occurring PKS genes and to identify the naturally occurring PKS genes and segments thereof.

Further, Applicants respectfully draw the Examiner's attention to the following definition of the term "polypeptide segment" in Paragraph [0072]:

> As used herein, the term 'polypeptide segment' can be used to refer a polypeptide sequence of interest. A polypeptide segment can correspond to a naturally occurring polypeptide (e.g., the product of the DEBS ORF 1 gene), to a fragment or region of a naturally occurring polypeptide (e.g., a DEBS module 1, the KS domain of DEBS module 1, linkers, functionally defined regions, and arbitrarily defined regions not corresponding to any particular function or structure), or a synthetic polypeptide not necessarily corresponding to a naturally occurring polypeptide or region.

Further, "[a] 'naturally occurring' PKS, PKS module, PKS domain, and the like is a PKS, module, or domain having the amino acid sequence of a PKS found in nature." (Paragraph [0083]). "A 'naturally occurring' PKS gene or PKS module gene or PKS domain gene is a gene having the nucleotide sequence of a PKS gene found in nature." Sequences of exemplary naturally occurring PKS genes are known (see, e.g., Table 12). (Paragraph [0084]).

These definitions not only provide support to the amendment made to claim 1 in this paper but also clearly teach a person of ordinary skill in the art what the term "reference polypeptide segment" in claim 1 refers to; thus, the structure of said "reference polypeptide segment" is within the grasp of a person of ordinary skill in the art in light of the well-known availability of the sequences of the naturally occurring PKS enzymes. Incorporating the structure of every reference polypeptide segment into the claim, as the Examiner has demanded, would be equivalent to incorporating the structure of every species into a genus compound claim, which is not only cumbersome but also unrealistic.

As the Court of Appeals for the Federal Circuit stated:

> a requirement that patentees recite known DNA structures, if one existed, would serve no goal of the written description requirement. It would neither enforce the quid pro quo between the patentee and the public by forcing the disclosure of new information, nor would it be necessary to demonstrate to a person of ordinary skill in the art that the patentee was in possession of the claimed invention.

Falkner v. Inglis, 79 USPQ2d 1001; 448 F3d 1357 (Fed Cir 2006). In this case, accessible literature sources, such as GenBank, clearly provide a person skilled in the art where to obtain

the structure of the reference polypeptide segment or the structure of the gene sequence encoding said reference polypeptide segment.

(B) As for the Examiner's second argument that "no functional limitation is recited in the claims for the recited 'polypeptide segment' described as being 90% or less or at least 95%, thus no correlation is made between function and structure," Applicants have not been able to see the relevance of the argument.

As an initial matter, claim 1, as well as the claims dependent from claim 1, is directed to a synthetic gene, not a "polypeptide segment" per se; thus, whether there is a functional limitation recited in the claim for the recited "polypeptide segment" is irrelevant. What claim 1 is concerned about is a synthetic gene that is capable of encoding a polypeptide segment corresponding to a reference polypeptide segment of a naturally occurring PKS. If the Examiner refers the "functional limitation" to that of the polypeptide segment encoded by the synthetic gene claimed, Applicants respectfully submit that such a "functional limitation" is in the claim, that is, "d) the polypeptide segment encoded by the synthetic gene retains the activity of the polypeptide segment encoded by the naturally occurring gene." This limitation is also recited in independent claims 86, 88, 91, and 93-95. If the Examiner refers the "functional limitation" to that of the synthetic gene, it is also clear that such a "functional limitation" is in the claim, that is, the synthetic gene must be capable of encoding a polypeptide segment that "corresponds to a reference polypeptide segment encoded by a naturally occurring polyketide synthase (PKS) gene," or in other words, the polypeptide segment encoded by the synthetic gene must retain the activity of the polypeptide segment encoded by the naturally occurring gene. In short, the instant invention is directed to synthetic genes that are functionally equivalent to the naturally occurring PKS genes although the sequences of the synthetic genes differ from those of the naturally occurring PKS genes significantly.

In fact, the activity of the naturally occurring PKSs has been well studied through analysis of various PKS modules, which has established the correlation between the polypeptide structure and function of the polypeptide segments that form the PKSs. (*See, e.g.,* paragraphs [0335]-[0351]). The instant invention was actually made based upon such established structure-function relationships to fulfill the goal of using synthetic genes to encode the functionally equivalent polypeptide segments of the PKSs to the naturally occurring PKSs and thus providing diverse pathways to this synthetically important class of enzymes.

Thus, Applicants respectfully submit that the functional limitation as suggested by the Examiner is present in the claims and the structure-function correlation is within the expertise of a person of ordinary skill in the art in view of the specification of this application.

(C) The Examiner's third argument is that the claims do not satisfy the written description requirement because "the claimed genus could include non-functional proteins or proteins with a different function than the one contemplated." Thus, the Examiner asserted that "the genus of claimed polypeptides encompass[] [sic] widely variant species. Based on the unlimited variations contemplated one skilled in the art would at best expect a protein that is different or at worst a protein that is not functional." Applicants respectfully submit that the Examiner has misread the claims.

As Applicants have emphatically stated before, the claims are directed not to a protein or polypeptide, but to a synthetic gene; thus the claimed genus does not encompass any, either "functional" or "nonfunctional," proteins or peptides per se. Apparent from claim 1, only a synthetic gene that encodes a polypeptide segment that corresponds to a reference polypeptide segment encoded by a naturally occurring PKS gene would fall into the scope of the claim. Claim 1, as well as other similar claims, also requires that "the polypeptide segment encoded by the synthetic gene retain[] the activity of the polypeptide segment encoded by the naturally occurring gene." In other words, if a synthetic gene encodes a polypeptide segment that does not function in the same way as the reference polypeptide segment encoded by a naturally occurring PKS gene, said synthetic gene would not fall in the scope of the claims here. Therefore, the Examiner's concern on the differently functional or non-functional proteins or peptides is a non-issue.

Moreover, 35 U.S.C. § 112, first paragraph does not require that all the species within a claimed genus to function in the same manner or to function at all. Therefore, whether a polypeptide or protein encoded by a synthetic gene would function in the same way as a polypeptide or protein of a naturally occurring PKS is irrelevant.

In short, the claimed genus does not include "non-functional proteins or proteins with a different function than the one contemplated" as the Examiner asserted. Thus, Applicants respectfully submit that the Examiner's concern is a result of misreading the claim language.

(D) The Examiner also states that "the specification fails to provide any additional representative species of the claimed genus to show that the application was in possession of the

claimed genus" (emphasis added). Applicants do not understand what "additional representative species" the Examiner refers to and why they should be required, because there is no such a requirement in 35 U.S.C. § 112.

As noted previously, Applicants have disclosed a new method for making synthetic genes encoding polypeptide segments corresponding to those encoded by naturally occurring PKS genes, and the synthetic genes made by this new method. In the specification, Applicants have provided synthetic genes with over 85,000 base pairs as examples of the synthetic genes claimed. To illustrate, the specification provides a detailed description of several synthetic genes made according to the invention (*see, e.g.,* Examples 7 and 9 and Tables 14A-B and 17A). These synthetic genes encode nine large polypeptides (ranging from about 1,410 amino acids to more than 7,000 amino acids in length) with > 99.7 % sequence identity with the corresponding naturally occurring polypeptide but only 74-76% sequence identity with the naturally occurring genes. In addition, to identify useful sites in PKS modules, Applicants have analyzed and aligned the amino acid sequences of 140 modules taken from 14 PKS genes. (Paragraphs [0476] and [0483]).

Applicants respectfully submit that these specific examples have made it reasonably clear to one of skill in the art, who is equipped with general knowledge of the genetic code and the relationship between DNA and amino acid sequences and guided by the teachings of the specification, that Applicants had possession of the invention claimed. Therefore, the Examiner's demand on disclosing "additional representative species" is unfounded.

In summary, the Examiner's concerns have already been answered by the disclosure with the specificity required by the statute.

Nevertheless, to further address the Examiner's concern on the term "reference polypeptide segment" in claim 1 and to expedite the prosecution, Applicants have amended claim 1 by defining the "reference polypeptide segment" as "selected from any polypeptide segments of a naturally occurring PKS." Further, the "naturally occurring PKS" is defined as "selected from the group consisting of erythromycin PKS, megalomicin PKS, oleandomycin PKS, pikromycin PKS, niddamycin PKS, spiramycin PKS, tylosin PKS, pimaricin PKS, pte PKS, avermectin PKS, oligomycin PKS, nystatin PKS, and amphotericin PKS." These PKSs have been chosen as the sources of 140 modules in initial analyzed set (Table 12). The amino acid sequences of these naturally occurring PKS enzymes are well studied; and so are the genes

encoding them, as disclosed in the specification: "Other sequences of domains, modules and ORFs of PKSs and PKS-like polypeptides can be obtained from public databases (e.g., GenBank)." (Paragraph [0499]). Therefore, the Examiner's concerns are hereby addressed thoroughly.

In view of the above arguments and the new amendment, Applicants respectfully submit that the pending claims 1, 3-5, 8-15, 69-74, 76, 79-89, and 91-95 of the instant application, at least as amended, comply with the written description requirement under 35 U.S.C. § 112, first paragraph, and respectfully request the Examiner to withdraw this ground of rejection.

II. Rejection Under 35 U.S.C. § 112, Second Paragraph (Indefiniteness) Should Be Withdrawn.

The Examiner rejected claims 1, 3-15 and 69-95 as allegedly non-compliant with the definiteness requirement under 35 U.S.C. § 112, second paragraph based upon the following assertions: (1) the term "synthetic gene" is indefinite because "it is unclear how to distinguish a stretch of sequence that is synthetic from the naturally occurring one"; (2) the recitation "a polypeptide segment that corresponds to a reference peptide" is indefinite because no structure of reference polypeptide is provided in the claims; and (3) the term "near" is indefinite because it is a relative term and it is unclear how "near" the restriction site is to the module. Applicants will address the Examiner's concerns in turn.

(1) In particular, the Examiner rejected claims 1, 85-86, 88, 90, 91, 93, 94, 95, and dependent claims thereof as indefinite for the recitation of "synthetic gene," asserting that "it [is] unclear how to distinguish a stretch of sequence that is synthetic from the naturally occurring one." (Final Office Action, page 5).

Applicants respectfully submit that the Examiner has misinterpreted the meaning of "indefiniteness" under 35 U.S.C. § 112, second paragraph. Under the statute, the term "indefiniteness" means that a term in a claim is ambiguous and thus subject to different interpretations. However, here the meaning of the term "synthetic gene" is clear and would not be susceptible to alternative interpretation(s) by a person of ordinary skill in the art.

Specifically, the term "synthetic gene" is defined as "a gene comprising a polypeptide segment-encoding sequence not found in nature, where the polypeptide segment-encoding sequence encodes a polypeptide or fragment or domain at least about 30, usually at least about 40, and often at least about 50 amino acid residues in length." (Specification, paragraph [0080]).

This definition itself has answered the Examiner's question "how to distinguish a stretch of sequence that is synthetic from the naturally occurring one." More specifically, the term "synthetic gene" in claim 1 has been defined as one "encoding a polypeptide segment, wherein said polypeptide segment corresponds to a reference polypeptide segment encoded by a naturally occurring polyketide synthase (PKS) gene," among others, with the following characteristics:

> c) the polypeptide segment-encoding sequence of the synthetic gene and the polypeptide segment-encoding sequence of the naturally occurring gene are less than 90% identical in nucleotide sequence; ... e) the polypeptide segment-encoding sequence of the synthetic gene is free from at least one Type IIS enzyme restriction site present in the polypeptide segment-encoding sequence of said naturally occurring gene; and f) the polypeptide segment-encoding sequence of the synthetic gene is different from the polypeptide segment-encoding sequence of said naturally occurring PKS gene and comprises at least two of: i) a Spe I site near the sequence encoding the amino-terminus of the module; ii) a Mfe I site near the sequence encoding the amino-terminus of a KS domain; iii) a Kpn I site near the sequence encoding the carboxy-terminus of a KS domain; iv) a Msc I site near the sequence encoding the amino-terminus of an AT domain; v) a Pst I site near the sequence encoding the carboxy-terminus of an AT domain; vi) a BsrB I site near the sequence encoding the amino-terminus of an ER domain; vii) an Age I site near the sequence encoding the amino-terminus of a KR domain; viii) an Xba I site near the sequence encoding the amino-terminus of an ACP domain." (For clarity, other limitations of claim 1 are omitted.)

Thus, difference between a "synthetic gene" claimed herein and a naturally occurring gene is clear.

The Examiner's real concern, as Applicants endeavor to make sense out of the Examiner's assertion, seems to be pertinent to a presumed technical difficulty to distinguish a synthetic gene from a naturally occurring one. Although Applicants do not believe this presumed technical difficulty would rise to the level of an "indefiniteness" issue under 35 U.S.C. § 112, second paragraph, nevertheless, Applicants would like to address the Examiner's concern.

First, Applicants respectfully submit, and hope the Examiner agrees, that given the state of the art in the area of protein and DNA sequencing when this invention was made, determination of a gene sequence or a polypeptide sequence had become a routine work for a person of ordinary skill in the art. Knowledge of DNA sequences of genes as complex as human genomes has become indispensable for basic research studying biological processes, as well as in applied fields such as diagnostic or forensic research. Indeed, automatic DNA sequencing systems have also become available, for example, the Rapid Analysis of Chromatograms

(Racoon) system disclosed in the specification (*see, e.g.,* section 10.2, paragraphs [0428]-[0445]). Similar advancement also exists in polypeptide sequencing. Using these systems, a person of ordinary skill in the pertinent art would be able to determine the sequence of a synthetic gene to the unit of a single nucleotide or amino acid and, thus, compare the same with a "naturally occurring one."

Second, in the instant application, claim 1, for example, is directed to a synthetic gene that differs from a naturally occurring PKS gene, which is known and available from various databases, by at least 10% in nucleotide sequence. The difference should be readily distinguished by the state of the art technology, as has been done by the present inventors (*see, e.g.*, Table 14A). Accordingly, Applicants respectfully submit that the term "synthetic gene" is not only clearly defined in the instant application but also readily distinguishable from the naturally occurring PKS genes, and therefore request the withdrawal of this ground of rejection.

(2) The Examiner rejected claims 1, 75, 85-86, 88, 90 and the dependent claims thereof as indefinite for the recitation of "a polypeptide segment that corresponds to a reference peptide," which allegedly is unclear because no structure of reference polypeptide is provided in the claims. As discussed in the previous section, the structure of said "reference polypeptide" is clear in light of the disclosure in the specification of the application, because the sequences of the naturally occurring PKSs are readily available. At least in the claim 1 as amended, the polypeptide sequences in the naturally occurring PKSs enumerated in the amended claim 1 are definite and clear to a person of ordinary skill in the art. From the limitations of the claims and the disclosure in the specification, Applicants respectfully submit that a person of ordinary skill in the art would understand the language of the claims and would be able to define metes and bounds of the claims by comparing the sequence of a synthetic gene and the polypeptide sequence encoded by the synthetic gene, respectively, with the sequences of the enumerated naturally occurring PKS genes and the sequences of the PKSs per se.

Thus, at least in view of the discussion in the previous section and the new amendment, Applicants respectfully request the withdrawal of this ground of rejection.

(3) The Examiner also maintained rejection of the original claim 7 allegedly due to the indefiniteness of the term "near." Due to cancellation of claim 7, this rejection has become moot. However, because the limitations of original claim 7 have been incorporated into other claims, such as independent claims 1, 86, 87, 91, and 93-95, in the interest of expedient

prosecution of this application, Applicants would like to address the Examiner's concern on this issue.

"Near" is indeed a relative term, as the Examiner has asserted; however, the term should be read and interpreted in the context in which the term is used. In this application, the term "near" is not just an ordinary relative term, because the term has been clearly defined in the specification as follows:

> A sequence motif or restriction enzyme site is "near" the nucleotide sequence encoding an amino- or carboxy-terminus of a PKS domain in a module when the motif or site is closer to the specified terminus (boundary) than to the terminus (boundary) of any other domain in the module. A sequence motif or restriction enzyme site is "near" the nucleotide sequence encoding an amino- or carboxy-terminus of a PKS module when the motif or site is closer to the specified terminus (boundary) than to the terminus of any domain in the module.

(Paragraph [0090]). Moreover, the restriction sites enumerated in the claims have also been described in great detail in paragraphs from [0484] through [0494], including Tables 7-10. In fact, Table 7 even shows the nucleotide positions for each restriction site, as well as the amino acid sequence near that restriction site.

Accordingly, Applicants respectfully request the Examiner to withdraw this ground of rejection.

III. Rejection of Claims 1, 3-4, 6, 8-15, 69-71, and 92 over Khosla et al. under 35 U.S.C. § 102(b) Should Be Withdrawn.

The Examiner rejected claims 1, 3-4, 6, 8-15, 69-71, and 92 as anticipated by Khosla et al. (US 6,066,721, hereinafter "Khosla et al."). The rejection is not supported by the evidence.

The Examiner rejected the claims "based on the breath of the claims," which is unintelligible to Applicants. Applicants figure that the Examiner must have intended to make the rejections "based on the breadth (instead of breath) of the claims"; however, "breadth" of a claim by itself is not a sufficient ground for rejection under 35 U.S.C. § 102(b) so long as the subject matter sought to be patented is not "anticipated" by a single prior art reference. The 35 U.S.C. § 102(b) statute is recited (as the Examiner has recited several times): "A person shall be entitled to a patent unless: … (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country one year prior to the date of application for patent in the United States." In short, the prior art reference must have disclosed

the same invention. In other words, a rejection under 35 U.S.C. § 102(b) requires nothing less than that all the limitations of the claim rejected be disclosed in a single reference cited, which the Examiner must elaborate with specificity, not merely by pointing out certain aspects of the invention casually as the Examiner has done here.

In the rejections, the Examiner ostensibly recited all limitations of claim 1 but did not offer evidence to show that all the limitations of claim 1 are disclosed in Khosla et al. The Examiner stated in general terms that "[t]he instant claim 1 as set forth above can be read broadly since 'gene' comprises structures with or without a promoter and the claim reads on any gene cluster having a catalytic domain." (Office Action, page 7). While ignoring all the other limitations, simply due to the alternative relationship between the limitations e) and f), the Examiner stated: "thus finding the limitation of (e) is all that is required." (Office Action, page 7).

Applicants cannot see what basis, or logic, the Examiner has adopted in interpreting claim 1 in the above manner and making the above statements. Clearly, claim 1 is not directed to "any gene cluster having a catalytic domain." Instead, claim 1 is directed to a "synthetic gene encoding a polypeptide segment, wherein said polypeptide segment corresponds to a reference polypeptide segment encoded by a naturally occurring polyketide synthase (PKS) gene." Moreover, the synthetic gene of claim 1 possesses, *inter alia*, the following characteristics: (a) the polypeptide segment encoded in the synthetic gene and the polypeptide segment encode by the naturally occurring gene are the same length and comprise at least 50 amino acids; (b) the polypeptide segment encoded in the synthetic gene and the polypeptide segment encoded by the naturally occurring gene are at least 95% identical in amino acid sequence; and (c) the polypeptide segment-encoding sequence of the synthetic gene and the polypeptide segment-encoding sequence of the naturally occurring gene are less than 90% identical in nucleotide sequence." None of these limitations have been disclosed by Khosla et al. Applicants respectfully submit that, when making rejections, the Examiner is not authorized to interpret a claim by reading only a portion of the preamble while ignoring all the other limitations recited in the claim.

The Examiner further stated:

> Khosla et al. teach methods to prepare a polyketide synthase gene cluster in which the ketosynthase domain in module 1 (KS1) is inactivated (see claim 1 and paragraph 11 of the patent), thus producing a mutated or modified gene cluster. In

> addition, Khosla et al. teach a recombinant plasmid vector which comprises an expression system for production of polyketide synthase (PKS) wherein said expression system comprises a nucleotide sequence encoding a functional modified modular PKS operatively linked to control sequences for expression of said modified PKS containing at least a first and second module, (wherein said modification inactivates the ketosynthase (KS) catalytic domain of the first module), thus anticipates claims 1, 3-4, 8-9 and 11-15.

(Final Office Action, pages 7-8). Applicants do not understand how the Examiner could make such a sweeping rejection of the claims without even pointing out any element in the rejected claims that is allegedly disclosed by Khosla et al. Khosla et al. does not even teach or address "naturally occurring PKS genes," let alone the limitations (a) through (f) enumerated in claim 1.

The Examiner asserted that "claim 6 is also anticipated since Khosla et al. is silent on Type IIS enzyme restriction, thus would meet the claim limitation of being 'free' of said restriction enzyme." First, as discussed above, even the independent claim 1 itself is not anticipated by Khosla et al., let alone the dependent claim 6 which depends from claim 1. Applicants respectfully submit that the Examiner's logic in making the rejection is faulty. Now that the limitations of the original claim 6 have been incorporated into the independent claim 1, Applicants would like to address the defects of the Examiner's reasoning on this specific issue. Simply because "Khosla et al. is silent on Type IIS enzyme restriction," it does not mean that "the polypeptide segment-encoding sequence of the synthetic gene is free from at least one Type IIS enzyme restriction site present in the polypeptide segment-encoding sequence of said naturally occurring gene." In Khosla et al., even if assuming it does disclose a synthetic gene, the synthetic gene could very well contain a Type IIS enzyme restriction site, because it does not affirmatively claim "free of" a Type IIs enzyme restriction site. On the contrary, the present invention affirmatively so claims. On this aspect alone, the instant claim 1 is distinguishable from Khosla et al.

The Examiner stated further: "Khosla et al. teach that said inactivation is by modification of a single codon of said catalytic domain, wherein said codon, in its unmodified form, encodes cysteine, and wherein said codon in its modified form encodes alanine (...), thus a preferred codon is selected." Applicants do not see the relevance of this statement to the claims of the instant application. Even if the facts were relevant, they do not teach any limitations of claim 1. The same can be said about the Examiner's statement "Khosla et al. teach a vector wherein said

modules are modules of the erythromycin PKS gene cluster." Merely because Khosla et al. has mentioned "erythromycin PKS gene cluster," plus the fact that erythromycin PKS gene is among the naturally occurring PKS genes the instant invention can use as a reference, it still does not teach any limitations of the instant claim 1.

Moreover, the Examiner stated: Khosla et al. "also discloses that the control sequences are heterologous to the encoding nucleotide sequence," and thus made an abrupt conclusion that "the limitations of the claims are met by the reference." Without the Examiner's elaboration, Applicants are left to wonder what "limitations of claims" are met by the reference; nor could Applicants see the relevance of the fact stated by the Examiner or logic that would support the Examiner's assertion.

As Applicants respectfully stated before, in order to anticipate a claim, a single reference must disclose all limitations of that claim. In the instant case, the Examiner has failed to point out many limitations of claim 1 that can also be found in Khosla et al., for example, any of the enumerated limitations (a) through (d), let alone the combination of them all, and limitation (e) or (f). Nevertheless, in the interest of expediting the prosecution of the instant application, claim 1 has been amended by changing the alternative term "or" to the conjunctive term "and" between limitations (e) and (f), as the Examiner has impliedly suggested. Khosla et al. has not disclosed either of the limitations (e) or (f), let alone the combination of the both.

Therefore, in view of the arguments above and the new amendments, Applicants respectfully request the withdrawal of rejections of the pending claims 1, 3-4, 8-15, 69-71, and 92 under 35 U.S.C. § 102(b).

IV. Rejection of Claims 1, 3-4, 6, 8-15, 69-71, and 92 over Katz et al. under 35 U.S.C. § 102(b) Should Be Withdrawn.

The Examiner rejected claims 1, 3-4, 6, 8-15, 69-71, and 92 as anticipated by Katz et al. again allegedly "based on the brea[d]th of the phrase 'synthetic gene' recited in the claims." The Examiner stated: "The term gene can be broadly interpreted as having a promoter or not and the term 'synthetic' can demonstrate the hand of man using PCR or codon optimization or genetic engineering. The claim can thus be broadly read as 'a polynucleotide encoding a polypeptide segment…'." Similarly to the rejection of claims made over Khosla et al. above, based on the alternative relationship between limitations (e) and (f) in claim 1, the Examiner concluded that "finding the limitation of (e) is all that is required." (Final Office Action, page 8).

Again, the Examiner has ignored most of the limitations of claim 1, as well as the claims dependent therefrom. In a sense, claim 1 is directed to "a polynucleotide encoding a polypeptide segment," as the Examiner has asserted, because a "synthetic gene" is a "synthetic polynucleotide," but Applicants do not understand how the claim can be so "broadly read" by ignoring all the other limitations, simply because "the term 'synthetic' can demonstrate the hand of man using PCR or codon optimization or genetic engineering."

As Applicants have repeatedly stated, claim 1 of the instant application is directed to a "synthetic gene encoding a polypeptide segment, wherein said polypeptide segment corresponds to a reference polypeptide segment encoded by a naturally occurring polyketide synthase (PKS) gene." Moreover, the synthetic gene of claim 1 possesses, *inter alia*, the following characteristics: (a) the polypeptide segment encoded in the synthetic gene and the polypeptide segment encode by the naturally occurring gene are the same length and comprise at least 50 amino acids; (b) the polypeptide segment encoded in the synthetic gene and the polypeptide segment encoded by the naturally occurring gene are at least 95% identical in amino acid sequence; and (c) the polypeptide segment-encoding sequence of the synthetic gene and the polypeptide segment-encoding sequence of the naturally occurring gene are less than 90% identical in nucleotide sequence. None of these elements have been disclosed by Katz et al.

The Examiner stated:

> Katz et al. teach a method to produce novel polyketide structures by designing and introducing specified changes in the DNA governing the synthesis of the polyketide accomplished by introducing one or more specified changes into the DNA sequence, thus a synthetic gene. The method of Katz et al. is disclosed as most useful when the segment of the chromosome modified is involved in polyketide biosynthesis, particularly for manipulation of polyketide synthase genes (derived from *erythromycin*), see columns 2-3 of the patent. Katz et al. also teach PKS domains such as AT and ACP, and teach PKS modules (see column 3 of the patent).

(Final Office Action, page 10, emphasis original). Although the Examiner has attempted to characterize Katz et al. as directed to a "synthetic gene," Katz et al. differs from the instant invention in several aspects. Katz et al. is directed to a "method for directing the biosynthesis of specific macrolide polyketide analogs by genetic manipulation of a polyketide-producing microorganism." (Column 1 or claim 1 of the patent). Katz et al. produces new polyketide molecules by "introduction of specific genetic alterations of the eryA sequence into the *Sac.*

erythraea." (Katz et al., column 4, lines 61-64). All alterations made in the gene sequences is done in the microorganisms. Even Katz et al. itself stated: "***In its broadest sense***, the present invention entails a general procedure for producing novel polyketide structures *in vivo* by selectively altering the genetic information of the organism that naturally produces a related polyketide." (Col. 4, lines 26-29, emphasis added). In contrast, the present invention, in one aspect, provides a method of cloning naturally occurring PKS genes by synthetic methods. Although Katz et al. involves isolation of various polynucleotide segments, none of them would satisfy the limitations of claim 1 in the instant application. Even if assuming the Examiner were correct about Katz et al. on its disclosure of "synthetic genes," the synthetic genes of Katz et al. do not read on claim 1 of this application, because Katz et al. does not mention any of the limitations enumerated in claim 1 here.

Although the Examiner has asserted that "Katz et al. is silent on 'TypeIIS,' thus would inherently be 'free of TypeIIS'," as discussed above, this statement is entirely based on a faulty logic, because in the absence of affirmative negation a synthetic gene in Katz et al. can contain a Type IIS restriction site. In contrast, the present invention is free from, not merely silent on, a Type IIS restriction site, and this point alone can distinguish the instant invention from the disclosure of Katz et al.

The Examiner further made various statements either irrelevant to claim 1 of the instant application or lack of elaboration on how they could be related to any limitations of the claim 1. For example, the Examiner stated: "Katz et al. utilizes restriction enzymes such as SphI and PstI," but this fact does not teach any limitations of claim 1, including (f) as the Examiner may have purportedly attempted to show. The Examiner's statement that "Katz et al. discloses a gene cluster 6-deoxyerythronolide from S. erythaea (...), which has a native thioesterase II" does not have any bearing to the limitations of the claim 1 here. In addition, the Examiner asserted that "[c]laims directed to vectors and host cells are anticipated since expression vectors and cells are used in the patent (referring to Katz et al.)," but this statement is, again, based on a faulty logic and has no bearing on any of the limitations in the independent claim 1. Finally, by asserting that "claims reciting a synthetic gene with a certain percent identity to the encoding gene are anticipated since following manipulation of the DNA structure the gene of Katz et al. would not be 100% identical to the native structure," (Final Office Action, page 10), the Examiner concluded that "the limitations of the claims are met by the reference." Applicants would like to

ask: what "limitations of the claims" are met by the reference? To make a rejection under 35 U.S.C. § 102(b), the Examiner has the burden to specifically point out a single prior art reference has disclosed each and every limitation of the claim. Applicants respectfully submit that the Examiner has failed to meet this burden. For example, the Examiner has failed to elaborate on where in Katz et al. each of the following limitations (a) through (f) is disclosed.

Moreover, even if assuming the Examiner had correctly asserted that "following manipulation of the DNA structure the gene of Katz et al. would not be 100% identical to the native structure," but this assertion does not satisfy the limitation (c) of claim 1, which is recited: "the polypeptide segment-encoding sequence of the synthetic gene and the polypeptide segment-encoding sequence of the naturally occurring gene are less than 90% identical in nucleotide sequence."

Further, the independent claims as amended require that at least two of the following must be present in the synthetic polynucleotide sequence comprising the recited polypeptide fragment:

i) a Spe I site near the sequence encoding the amino-terminus of the module;
ii) a Mfe I site near the sequence encoding the amino-terminus of a KS domain;
iii) a Kpn I site near the sequence encoding the carboxy-terminus of a KS domain;
iv) a Msc I site near the sequence encoding the amino-terminus of an AT domain;
v) a Pst I site near the sequence encoding the carboxy-terminus of an AT domain;
vi) a BsrB I site near the sequence encoding the amino-terminus of an ER domain;
vii) an Age I site near the sequence encoding the amino-terminus of a KR domain;
viii) an Xba I site near the sequence encoding the amino-terminus of an ACP domain.

If at all, Katz et al. discloses only the use of Pst I site within a primer to clone "1.4 kb segment of eryA, between sequence coordinates 1.11-2.54 (fragment 5)," whereas the limitation (f) of claim 1 of this application requires as least two of the enumerated restriction sites. In addition, Katz et al. does not disclose whether the Pst I sequence is present in the gene obtained, nor the same location as is described in the claim 1 of the instant application.

As stated above, in the interest of expediting the prosecution, Applicants have amended claim 1, while preserving the right to prosecute the claims as their current state in the future, by changing the relationship between limitations (e) and (f) from alternative to conjunctive, as suggested by the Examiner.

Accordingly, in view of the arguments above and the amendment presented, Applicants respectfully request the Examiner to withdraw the rejections of claims 1, 3-4, 8-15, 69-71, and 92.

V. Rejections under 35 U.S.C. § 103(a) over Katz et al. in view of Kim et al. Should Be Withdrawn.

The Examiner rejected claims 1, 3-15, 69-71, 74, 75, 77-82, and 85-95 as allegedly obvious over Katz et al. in view of Kim et al. (*Gene*, 199: 293-301, 1997)(hereinafter "Kim et al."). Applicants respectfully submit that the Examiner has failed to establish *prima facie* obviousness of the claims.

The Examiner relied on Katz et al. as the primary reference in making the 35 U.S.C. § 103(a) rejections. The Examiner essentially repeated the assertions made in the 35 U.S.C. § 102(b) rejections over Katz et al. above. As discussed above, Katz et al. does not teach any of the limitations (a) through (f) enumerated in claim 1 of the instant application. Again, in the rejections of the claims, the Examiner has not discussed how Katz et al., or its combination with Kim et al., teaches a person of ordinary skill in the art any of the enumerated limitations. The Examiner has made numerous assertions on obviousness issue by a personal subjective standard without concrete evidence, just listing a few: (1) "Katz et al. renders obvious claims directed to vectors and host cells since expression vectors and host cells are used in the patent"; (2) "Katz et al. also render obvious claims reciting a synthetic gene with a certain percent identity to the encoding gene since following manipulation of the DNA structure the gene of Katz et al. would not be 100% identical to the native structure"; and (3) "claims reciting a length of at least 100 amino acid residues is also obvious since the phrase 'at least' has no upper boundary and the structure of the encoding genes are well established in the art."

Applicants respectfully submit that the Examiner's sweeping language does not meet the standard required by the statute because it fails to consider the limitations of claims. If the Examiner's first assertion were true, it would mean that as long as some examples were disclosed in the prior art, then any examples falling into the same category would become obvious. To analogize the Examiner's assertion that "Katz et al. renders obvious claims directed to vectors and host cells since expression vectors and host cells are used in the patent," it would follow that simply because some organic compounds were disclosed in a prior art reference, then any other organic compounds would become obvious regardless of the structures and/or functions of these

respective compounds. Likewise, simply because Katz et al. has made some changes to some DNA structures, thus resulting some DNA structures not 100% identical to the original DNA structures, it does not follow that change of another DNA structure by whatever percentage would become obvious. The Examiner is reminded again that claim 1 of the instant application is directed to a synthetic gene with less than 90% identity to a naturally occurring PKS gene while it can retain encoding ability to produce substantially the same polypeptide sequence. This unique feature is not obvious over Katz et al or its combination with Kim et al.

As discussed above, all the independent claims directed to synthetic genes have been amended to include limitations (e) and (f) from alternative relationship to conjunctive relationship. Neither Katz et al. nor Kim et al., or combination of the both, disclose or suggest these additional limitations. Specifically, as the Examiner has acknowledged, Katz et al. is silent on the removal of at least one Type IIS enzyme restriction site present in the polypeptide segment-encoding sequence of the naturally occurring gene (see Final Office Action, page 10), and therefore, it does not teach limitation (e). With regard to limitation (f), likewise, Katz et al. is also silent on the presence of the enumerated specific restriction sites, let alone the locations of these recognition sites; thus Katz et al. does not teach limitation (f). Neither would Kim et al. suggest a person of ordinary skill in the art to make a synthetic gene with such characteristics.

Kim et al. deals with a completely different gene (erythropoietin) and only discloses that the gene optimized with human codons in human cell expresses at a higher level than that optimized with yeast codons. Kim et al. addresses codon optimization for increased expression of the target protein and does not address the selection of codons for introduction of restriction endonuclease recognition sites. As a person of ordinary skill in the art would realize, a codon optimization for increased expression would not necessarily yield the codons forming a restriction endonuclease recognition site.

As in the section 102(b) rejections discussed above, here the Examiner has read the claim 1, again, broadly as being directed to "a synthetic gene encoding a polypeptide that corresponds to a reference peptide encoded by a naturally occurring PKS gene," while ignoring all the other limitations. For example, the Examiner's major conclusory assertions are recited in the following paragraph:

> ... Therefore, it would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to have a synthetic gene encoding a polypeptide ... for example *because Katz et al. teach the manipulation of PKS*

> *gene structures and Kim et al. teach codon optimization for enhancement of synthetic genes.* ... Thus, one of ordinary skill in the art would be motivated to produce a synthetic gene with a reasonably expectation of success based on the teachings of Katz et al. *because the reference demonstrates the manipulation of gene structures encoding known proteins and Kim et al. as well as the instant specification acknowledges the usage of codon optimization to enhance the expression of a protein of interest.* ... One of ordinary skill in the art would be motivated to combine the teaching of Katz et al. and Kim et al. *because Kim et al. teach that since the gene optimized with human codons in human cell expresses at a higher level than that optimized with yeast codons, the ordinary skill in the art would have come to the conclusion that optimizing the signal peptide coding sequence with human codons would enhance the expression even further.*

(Final Office Action, pages 13-15, emphasis added). It is apparent that all of the Examiner's assertions have failed to address the "obviousness" issue of the specific limitations of claim 1. Even if assuming that 35 U.S.C. § 103(a) would not require that all the limitations be taught specifically by the references cited, the statute in the minimum requires that the references cited render all the limitations of the rejected claim obvious. Applicants respectfully submit that the references cited by the Examiner do not meet this minimum requirement.

For example, even assuming, but without admitting, that the references cited by the Examiner disclose that the restriction enzyme recognition sites may be introduced into the synthetic gene, a broad disclosure does not necessarily make obvious specific species or subgenus, in particular when the species or subgenus possesses some unique features that would not be shared by the genus broadly disclosed. Specifically, in the instant case, the references do not disclose or suggest introducing restriction sites for the eight specific enzymes at eight specific locations within the claimed synthetic gene, as in limitation (f) of claim 1.

Accordingly, even for limitations (e) and (f) alone, the claim 1 as amended would not be obvious over Katz et al. in view of Kim et al. Likewise, neither are claims 85, 86, 88, 90, 91, and 93-95, or any of the dependent claims, obvious.

Therefore, Applicants respectfully request the withdrawal of the rejections of claims 1, 3-5, 8-15, 69-74, 79-82, and 85-89, and 91-95 under 35 U.S.C. § 103(a).

VI. Comments on the Examiner's Responses to Applicants' Previous Arguments

The Examiner has responded to Applicants' previous Amendment and Response dated December 31, 2008, in reply to the previous office action. Applicants address the Examiner's various arguments in turn as follows.

First, in response to Applicants' argument that "it should be within ordinary skill in the art to access the amino acid and nucleotide sequences of naturally occurring PKS gene, which are available in multiple databases and to identify the naturally occurring PKS genes and segments thereof," the Examiner argued that "there is no structure-function correlation made in the claims or specification for the large variable genus claimed" because the language of limitation (c) in claim 1 "encompasses structures such as 85%, 75%, 65%, 55%, 45%, 35%, 25%, 15%, 5%, 1%, 0% etc." (Final Office Action, page 16).

Applicants have failed to see the logic of the Examiner's argument. First, the Examiner has again misread, or misinterpreted, the claim limitations. Referring to the limitation (c) of claim 1, the Examiner asserted that "claim 1 for example is directed to a polypeptide segment-encoding sequence of the synthetic gene and the polypeptide segment-encoded by the naturally occurring gene are less than 90% identical in nucleotide sequence" (Final Office Action, page 16, emphasis added), but in fact the limitation (c) of claim 1 is that "the polypeptide segment-encoding sequence of the synthetic gene and the polypeptide segment-encoding sequence of the naturally occurring gene are less than 90% identical in nucleotide sequence." Applicants respectfully draw the Examiner's attention to the two highlighted portions above. In limitation (c) of claim 1, the sequence of a synthetic gene is compared with a sequence of a naturally occurring gene, whereas in the Examiner's assertion the sequence of a synthetic gene is compared with a sequence of a polypeptide segment encoded by a naturally occurring gene.

Applicants do not speculate whether the Examiner's questionable assertion is a result of the misreading or misinterpretation of the claim limitation; nevertheless, the Examiner's statement "there is no structure-function correlation made in the claims or specification for the large variable genus claimed" is confusing. Limitation (c) is but one of a number of limitations enumerated in claim 1, and the claim also requires, among others, that (b) the polypeptide segment encoded by the synthetic gene and the polypeptide segment encoded by the naturally occurring gene are at least 95% identical in amino acid sequence"; and (d) the polypeptide segment encoded by the synthetic gene retains the activity of the polypeptide segment encoded by the naturally occurring gene." Therefore, Applicants respectfully submit that the correlation between structure (synthetic gene) and function of the synthetic gene is clearly disclosed.

Moreover, even if assuming the Examiner has correctly stated that the language of the limitation (c) encompasses synthetic genes whose sequences are 85%, 75%, 65%, 55%, 45%,

35%, 25%, 15%, 5%, 1%, or 0% identical to a sequence of a naturally occurring PKS gene, Applicants cannot see why this fact would affect the patentability of the claim. On the contrary, if a hypothetical synthetic gene dramatically different from a naturally occurring gene structurally, say, only 5% identical in nucleotide sequence, could encode a polypeptide segment substantially same as the polypeptide segment encoded by the naturally occurring gene both structurally and functionally, Applicants respectfully submit that the hypothetical synthetic gene would be highly innovative and thus patentable.

Second, the Examiner cited various cases to support the argument that adequate written description is required to satisfy 35 U.S.C. § 112, first paragraph. As the cases and the MPEP dictate, and the Examiner has alluded to, the standard for the written description requirement is whether an application has made sufficient disclosure that would lead a person of ordinary skill in the art to the conclusion that the applicant was in possession of the invention. (*See, e.g.*, Final Office Action, page 19, citing MPEP § 2163). Pursuant to the extensive discussion presented in Section I above, Applicants believe that the Examiner's concerns on this issue have been addressed thoroughly. In short, the detailed methods for preparing the synthetic genes as claimed are disclosed in the specification, from design of the synthetic genes (paragraphs [0131] through [0144]) to synthetic steps (paragraphs [0145] through [0225]), as well as computer-aided design and synthesis of the genes. Moreover, plenty of examples have been provided to show that Applicants had possession of the invention. The examples include various synthetic genes encoding 6-deoxyerythronolide B synthases ("DEBS") and synthetic genes encoding epothilone A synthase, including disclosure of their nucleotide sequences and the comparison with the corresponding naturally occurring gene sequences, as well as comparison of the polypeptide sequences encoded by these synthetic genes with those of the naturally occurring PKSs. (*See, e.g.,* Table 14A through Table 17B, and related text and sequences).

At least in view of the new amendments of the claims, Applicants respectfully submit that the examples disclosed are sufficient to lead a person of ordinary skill in the art to the conclusion that Applicants possessed the invention as claimed.

Third, in the Examiner's response to Applicants' arguments concerning the rejection under 35 U.S.C. § 112, second paragraph, the Examiner has again misread Applicants' statement. The Examiner asserted that Applicants had stated that "... the gene segment should only differ by 10%" (Final Office Action, page 20, second full paragraph)(emphasis added), but

in fact Applicants stated the opposite, as recited: "The claims specifically recite that the nucleotide sequence of the claimed gene segment should differ by at least 10% from the polynucleotide sequence of the naturally occurring reference genes." (*See* Applicants' "Amendment and Response" of December 31, 2008, page 10, top)(emphasis added).

The Examiner stated that "independent claim 1 for example has to stand on its own and does not presently have a structural limitation with the recited percent language." (Final Office Action, pages 20-21) Applicants respectfully note that the claim should not be read in vacuum. The test for definiteness under 35 U.S.C. 112, second paragraph, is whether "those skilled in the art would understand what is claimed when the claim is read in light of the specification." *Orthokinetics, Inc. v. Safety Travel Chairs, Inc.*, 806 F.2d, 1565, 1576 (Fed. Cir. 1986). In the present application, the "percent language" has clearly set forth what are the metes and bounds of the claim limitation.

Fourth, the Examiner maintained rejection of the term "near" as indefinite merely due to its relative nature. As discussed above, the term "near" has been clearly defined in the specification. "An applicant is entitled to be his or her own lexicographer and may rebut the presumption that claim terms are to be given their ordinary and customary meaning by clearly setting forth a definition of the term that is different from its ordinary and customary meaning(s)." MPEP 2111.01.IV (citing *In re Paulsen*, 30 F.3d 1475, 1480, 31 USPQ2d 1671, 1674 (Fed. Cir. 1994)). "The specification should also be relied on for more than just explicit lexicography or clear disavowal of claim scope to determine the meaning of a claim term when applicant acts as his or her own lexicographer; the meaning of a particular claim term may be defined by implication, that is, according to the usage of the term in the context in the specification." MPEP 2111.01.IV (citing *Phillips v. AWH Corp.*, 415 F.3d 1303, 75 USPQ2d 1321 (Fed. Cir. 2005) (en banc)).

In this case, the term "near" is clearly defined with respect to the location of the enumerated restriction sites in the gene sequence (*see* Section II above). As for the Examiner's statement that "the limitations of the specification cannot be read into the claims," Applicants respectfully submit that the Examiner has confused the issue of interpreting a claim term with another distinct issue, namely incorporating limitations into a claim from specification. Interpreting an otherwise "indefinite" term by resort to the definition of the term in the specification is entirely different from incorporating a limitation into a claim from the

specification. The former is not only justified but often necessary in the interpretation of claim terms, whereas the latter refers to unjustly broadening or narrowing of the scope of a claim. In the instant case, Applicants merely request the Examiner to read the term "near" in light of its definition set forth in the specification, entirely unrelated to broadening or narrowing the scope of the claim itself.

Finally, the Examiner maintained the rejection of claim 1 based on the references cited allegedly due to the alternative relationship between limitations (e) and (f). As discussed above, none of the references, or combinations thereof, have taught or suggested either limitation (e) or limitation (f), as well as other enumerated limitations. However, in the interest of expediting the prosecution, Applicants have taken the Examiner's suggestion by amending claim 1 as presented above. At least the new amendment has overcome the Examiner's rejection on this ground.

In sum, Applicants have addressed all the Examiner's concerns regarding this application and have overcome all the claim rejections and thus respectfully request the Examiner to withdraw the rejections to the pending claims in light of the amendments and arguments presented above.

CONCLUSION

In view of the new amendments and remarks presented above, Applicants believe that the claims of this application are in condition for allowance and an early notice to this effect is earnestly solicited. If the Examiner does not believe that such action can be taken at this time or if the Examiner feels that a telephone interview is necessary or desirable, Applicants welcome the Examiner to call the undersigned at 609-844-3020.

The USPTO is authorized to charge Deposit Account No. 50-1943 for any charges in connection with this matter.

Respectfully submitted,

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